REMARKS

Claims 1, 10 and 85-105 are pending in the application and have been rejected.

Claims 1 and 10 have been amended to specify that the calcium-sensing receptor expressing cells are hematopoietic cells and claims 86 and 100 have been amended to clarify that the hematopoietic cells of claims 1 and 98 (which depends on claim 10), respectively, are hematopoietic progenitor cells.

Claim 85 has been amended to specify that the hematopoietic cells are monocytes. Support for this amendment can be found, for example, throughout Example 1.

Claim 105 has been amended to remove dependencies from cancelled claims. No other amendments have been made.

Claims 87-90, 99 and 101-104 are now cancelled.

As described herein, support for the amended claims and new claim can be found throughout the application. No new matter is added. It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. §112. The amendments of and additions to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

Rejection under 35 USC §103

Claims 1, 10 and 85-105 are rejected under 35 U.S.C. §103(a) as unpatentable over Yamaguchi, *et al.* (*J. Bone and Mineral Research*, v. 13(10) 1998). Applicants respectfully traverse this rejection.

Yamaguchi teaches that CaR agonists stimulate chemotaxis of CaR expressing MC3T3-E1 cells (i.e., an osteoblastic cell line) *in vitro*. It is alleged that it would have been obvious to administer an agonist to a subject in order to facilitate migration of any known CaR positive cell with the reasonable expectation that the cells would migrate to the concentration of the agonists as shown *in vitro* by Yamaguchi. It is further alleged that "if agonists will effect migration, then antagonists will as well (page 3, paragraph 2 of the Office Action).

For the §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988). There must also be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993).

The teachings of Yamaguchi cannot be extended to CaR expressing hematopoietic cells of the invention, but rather are limited to osteoblastic cell lines. The discussion of Yamaguchi makes this limitation clear (page 1536, first paragraph):

> These findings suggest that a calcium-sensing mechanism is present in these osteoblastic cells and is involved in their migration and proliferation. In this study, we confirmed these previous observations and further showed that the CaR agonists, Gd^{3+} and neomycin, as well as high Ca^{2+} per se could induce chemotaxis of MC3T3-E1 cells.

Nowhere does Yamaguchi suggest that the findings with regard to chemotaxis can be extended to non-osteoblastic cells. In fact, according to Yamaguchi, there was debate in

the field as to whether other cells, such as monocytes, expressed the CaR receptor (page 1536, second paragraph).

Accordingly, Yamaguchi provides no reasonable expectation of success for the skilled practitioner to administer a nonCa^{++} CaR agonist to a subject in order to facilitate migration of a CaR expressing hematopoietic cell to a specific site in the subject. Such reasonable expectation of success can be found only in Applicant's disclosure, for example, on page 45, lines 15-24, where agonist-induced migration of CaR expressing monocytes *in vivo* is first described.

In this regard, the teaching in Yamaguchi falls short in at least two important aspects. First, Yamaguchi fails to teach or suggest that a nonCa^{++} CaR agonist could induce chemotaxis in a CaR expressing cell that is *not* an osteoblast. A fair reading of Yamaguchi indicates there is no suggestion for administration of a nonCa^{++} CaR agonist to a site *in vivo* with the expectation of enhancing migration of CaR receptor expressing hematopoietic cells to that site. Yamaguchi simply does not extend its proposed migratory function of the CaR receptor in MC3T3-E1 cells to other, non-osteoblasitc cells.

Second, in contrast to the instant specification, there is no teaching by Yamaguchi that a cell would be susceptible to *in vivo* treatment by a nonCa^{++} CaR agonist. Yamaguchi provides absolutely no showing of an *in vivo* effect, but merely speculates that the CaR expressing osteoblasts could play a role in skeletal remodeling. There is no indication that what was observed in MC3T3-E1 cells would work *in vivo*.

Thus, there is no reasonable expectation that the effects observed with primitive, early stage osteoblastic cell lines cultured *in vitro* would provide an expectation of a similar effect in CaR expressing hematopoietic cells *in vivo* by the administration of a nonCa^{++} CaR agonist.

The lack of predictability in transferring results or findings from cell culture studies to *in vivo* effects has long been admitted by the Patent Office. Generally, only a well-

documented animal model showing the same effects as *in vitro* studies has been accepted where methods or treatments are claimed for biological systems. In part this standard arises because there are numerous physiological factors interplaying in biological systems. In this case, predictability is speculative, the reference provides no guidance for *in vivo* use, and the "model" showed only that it was difficult to identify a CaR receptor in a primitive cell with no guidance or suggestion to administer an agonist or antagonist to a site in order to induce or prevent migration of CaR expressing hematopoietic cells to that site.

Furthermore, there was no incentive or motivation for the skilled practitioner to modify the teachings of Yamaguchi to encompass CaR expressing hematopoietic cells. As stated above, there was debate in the field as to whether other cells, such as monocytes, expressed the CaR receptor (page 1536, second paragraph). Thus, it was questionable whether other cells could function through the CaR receptor, much less function in precisely the same way as osteoblasts.

Applicants submit that the Yamaguchi reference does not teach or suggest the claimed invention. Removal of the reference as prior art and reconsideration of claims 1, 10, 85, 86, 91-98, 100 and 105 is respectfully requested.

Conclusion

Applicants believe that a complete response has been submitted and respectfully submit that this application is now in condition for allowance of claims 1, 10, 85, 86, 91-98, 100 and 105. Should any issues remain or should the Examiner believe that a telephone conference with Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to contact the undersigned at the telephone number shown below. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105.

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